ASSESSING THE RISK POSED BY RUBELLA TO PREGNANT TRAVELERS

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Abstract

Background

Rubella has been eliminated from the U.S. but remains endemic in some parts of the world. Given that vaccine uptake and effectiveness are below 100%, individuals in the U.S. may experience a non-zero risk of rubella infection, especially if they are to travel. This risk is particularly important for pregnant women since infection during pregnancy can result in adverse outcomes such as congenital rubella syndrome and fetal or neonatal death. Identifying socio-demographic groups at higher risk for susceptibility and quantifying country-specific risk of infection can help clinicians provide targeted recommendations regarding travel during pregnancy.

Methods

Using data from the 2009-2010 cycle of the National Health and Nutrition Examination Survey (NHANES), we evaluated overall prevalence of rubella susceptibility among women of reproductive age and in socio-demographic groups considered at highest risk for CRS as well as those most likely to travel during pregnancy. We also estimated the force of infection using a rubella transmission model to highlight areas to which prenatal travel may be inadvisable.

Results

Among 1,685 female NHANES participants aged 18-49 years in 2009-2010, prevalence of susceptibility to rubella, defined as an IgG ELISA result of <10 IU/mL, was 3.3%. Odds of susceptibility did not vary significantly by age, race/ethnicity, country of birth, citizenship status, or receipt of hepatitis A vaccine. Analysis of a subgroup of women

born outside of the U.S. showed no differences in susceptibility by length of time since moving to the U.S.

Among 147 countries evaluated by our transmission model, 43 had forces of infection at or above one infection per thousand person years. Areas with the highest forces of infection were those to where travel is relatively infrequent.

Conclusion

This study is one of few studies evaluating susceptibility to rubella among women of reproductive age in the U.S. in the post-elimination era. Rubella burden remains considerable in some countries, and pregnant travelers to these areas may be at particularly high risk for prenatal infection. Further studies are needed with larger samples to adequately evaluate differences in susceptibility by demographic and other characteristics in order to identify targeted interventions to decrease risk for CRS.

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Introduction

Rubella is a contagious viral disease that was declared eliminated from the U.S. in 2004 following dedicated and sustained efforts to induce population-level immunity through vaccination.[1,2] Despite the widespread availability of rubella-containing vaccines (RCVs) in many parts of the world, the virus remains a leading cause of vaccine-preventable birth defects worldwide.[3] This circumstance is attributable to several factors including the absence in many countries of routine vaccination for rubella, spatial heterogeneity in vaccine coverage within countries employing RCVs,[4] and migration or travel-associated rubella importation to areas where RCV coverage is below herd immunity thresholds.[5,6] In addition, the vaccine is considered 97% effective after one dose,[7] meaning some individuals remain susceptible despite having been vaccinated.

Based on the continuing endemicity of rubella observed in countries outside of the Americas and susceptibility to infection due to a lack of or incomplete immunization, women in the U.S. and their fetuses may experience a non-zero risk of rubella infection and consequently fetal congenital rubella syndrome (CRS), particularly if they travel internationally during pregnancy. Furthermore, current clinical practices and guidelines in the U.S. may leave gaps in risk minimization related to rubella and CRS. Antibody titers to the virus are typically measured at a woman's first prenatal visit in order to identify vulnerability to infection[8] but the vaccine is contraindicated during pregnancy and risk avoidance counseling is not necessarily provided to women who are found to be serologically naïve.[8]

Using data from NHANES 2009-2010, the objective of this study was to estimate overall susceptibility to rubella among women of childbearing age and to determine

whether women in this age group who are more likely than others to travel are at increased risk for non-immunity to rubella infection. In addition, we aimed to quantify a susceptible woman's likelihood of infection for various countries, as determined by country-level estimates of force of infection.

Rubella and Congenital Rubella Syndrome

Rubella has long been considered a disease of public health importance owing to its high level of infectiousness and its teratogenic effects on the gestating fetus. Postnatal transmission of the rubella virus occurs through the respiratory route, typically causing acute yet mild illness characterized by rash, low grade fever, and swollen lymph nodes appearing 2-3 weeks after initial exposure.[9] As many as 30% of infections acquired postnatally are never clinically apparent.[10]

Despite its relatively innocuous presentation in those acquiring infection postnatally, rubella causes substantial morbidity and mortality when expectant mothers are infected shortly before conception or in the first trimester of pregnancy.[10,11] Because the virus can cross the placenta and infect the fetus, cause systemic inflammation, and hinder organ development,[9,12] prenatal rubella infection can result in pregnancy loss, neonatal death, and other severe adverse outcomes. The fetus may be affected by congenital anomalies in up to 90% of maternal cases occurring in the first 11 weeks of pregnancy;[11] the presence of which are known in a rubella-positive neonate as congenital rubella syndrome, or CRS. CRS most commonly manifests in the optic lens (e.g., as cataracts), heart (as patent ductus arteriosus or peripheral pulmonary artery stenosis), or cochlea (as hearing impairment)[8] but can take other forms, as rubella has been shown to damage the brain, lung, liver, spleen, kidney, bone marrow, bones, and endocrine

organs.[13] In addition to heart disease and vision or hearing loss, infants with a CRS diagnosis may experience a host of other pathologies including hepatosplenomegaly, microcephaly, encephalitis, and/or developmental delays.[14] Throughout the globe, an estimated 100,000 infants are affected by CRS each year.[15]

In the pre-vaccine era, rubella was known to circulate in a pattern marked by yearly seasonal epidemics, with larger epidemics occurring every 6-9 years.[16] With this dynamic, most individuals susceptible at the start of a large epidemic would be infected by its end, resulting in an average age of infection of 9-11 years.[17] However, the introduction of a rubella-containing vaccine in 1969 changed the dynamics of rubella throughout much of the world, leading to decreases in both the force of infection and the annual number of incident rubella and CRS cases. As a result of systematic vaccination of infants and a vaccine campaign targeted toward adolescent girls and adult women, the last U.S. rubella epidemic occurred in 1964; forty years later, rubella was declared eliminated from the country.[10] In the meantime, other countries in the Western Hemisphere also scaled up rubella vaccination efforts in the interest of eliminating both rubella and CRS and consequently, the last known endemic case of rubella in the Americas occurred in Argentina in 2009. The WHO declared the virus eliminated from the region of the Americas in 2015.[18] Globally, more than 80 countries have eliminated rubella since RCVs were introduced.[18]

Despite the substantial progress made with respect to reductions in rubella and CRS, the virus continues to circulate in areas with no or low RCV coverage; worldwide, an average of 30% of children do not have access to these vaccines.[19] WHO has established recommendations for setting elimination goals for countries that have not

achieved rubella elimination,[20] however, a country's decision to implement these goals is not necessarily straightforward. With a vaccine effectiveness of 97%, it is estimated that depending on the birth rate in an area, between 77 and 87% of the population must be vaccinated from rubella in order to achieve local elimination.[21,22] Reaching these levels of immunity can prove challenging in countries where resources are limited, healthcare infrastructure is weak, or there exists spatial or temporal variability in the proportion immune. [6,23] In addition, because increased vaccination leads to decreases in the force of infection and consequently increases in the average age of infection, the public health impact of rubella can be made worse for pregnant women if vaccine coverage is inadequate for eliminating transmission, but is high enough that infections are expected to occur during the childbearing years.[24,25]

As of 2018, the WHO region of the Americas was the only of the six WHO regions to have achieved elimination,[19] defined as the absence of sustained rubella transmission for a period of at least one year.[26] The European and Western Pacific Regions have established elimination goals, while the South East Asia region has set a goal for rubella control.[19] The remaining two regions, the Eastern Mediterranean and Africa, have not yet established such goals.[19] In each of the two regions without goals for elimination or control, vaccine coverage remains below WHO's recommended threshold of 80%.[19] More specifically, in the African region, 27 (57%) countries have not added RCVs to their routine immunization schedules, and RCV coverage is low, at 32% for the region overall.[19] In the Eastern Mediterranean Region, 16 (76%) countries have introduced RCVs, but vaccine coverage is estimated at only 45%. South East Asia has implemented routine use of RCVs in 10 (91%) countries, and vaccine coverage is close to

the recommended threshold, at 83%.[19] Globally, a total of 26 countries have not introduced RCVs at all.[3] In recent years, the highest rubella burden has occurred in Africa and South East Asia.[15] As such, U.S. based travelers to these and other areas with low vaccine coverage may be at risk for infection and CRS.

Travel Advisories During Pregnancy

Travel advisories specific to pregnant women have been implemented by various health agencies for several infectious diseases over time. These advisories could play an important role in minimizing risk of rubella among pregnant women in the U.S., given that most known cases of rubella occurring in the U.S. since 2004 have been imported.[27] However, travel guidelines issued by these agencies do not currently provide guidance on travel to rubella-affected areas.

In 2005, the International Health Regulations, an agreement made by the 196 member countries of the WHO, established guidelines for maintaining global health security, including guidelines surrounding the implementation of recommendations for restricted travel.[28] Specifically, the purpose of the agreement is to "prevent, protect against, control, and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks," while avoiding unnecessary restrictions on travel and trade. The scope of the agreement is not limited to any particular diseases, but is intended to cover any "illness or medical condition, irrespective of origin or source, that presents or could present significant harm to humans."[28]

In congruence with the requirements set forth by the IHR, the CDC publishes the U.S. government's travel health guidelines[29], which include pretravel health evaluation

and destination-specific recommendations for pregnant travelers. At present, the CDC recommends that all pregnant women planning to travel are screened for immunity to rubella, though rubella susceptibility is not listed among its contraindications for travel.[29] Furthermore, though these guidelines emphasize risk of certain infectious diseases during travel (e.g., malaria, hepatitis A and E) and recommend against travel to Zika-affected areas, no emphasis is placed on risks related to rubella, despite the high probability of poor fetal outcomes among women experiencing infection early in pregnancy.

The American College of Obstetricians and Gynecologists (ACOG) publishes clinical guidance on women's health and pregnancy and issues recommendations to obstetricians for providing perinatal care. Testing recommendations for immunity to rubella during the first prenatal visit are included in their obstetrical practice guidelines, which typically occur during a woman's first trimester of pregnancy.[8] Under ACOG's recommendations, pregnant women found to be non-immune to rubella should be vaccinated in the postpartum period, but no further recommendations are provided with respect to management of rubella risk during pregnancy.[8] However, guidelines surrounding risk counseling and travel do seem to be within ACOG's purview, as the organization recommends counseling surrounding air travel and avoidance of travel to areas with endemic transmission of hepatitis A, malaria, or Zika.[8]

Risk Factors for Rubella and CRS

In the U.S., international travel has been strongly associated with rubella and CRS. Since 2004, approximately ten cases of rubella have occurred in the U.S. each year, and all cases since 2012 have been associated with foreign travel.[26,30] From 2005-2017,

fifteen U.S.-born infants were diagnosed with CRS, and most were born to mothers known to have traveled during pregnancy.[14]

I reviewed published case reports describing CRS diagnosed in infants born in the U.S. between 2004 and 2020 in order to identify risk factors for CRS in the post-elimination period. Six reports describing eight CRS incidents diagnosed in the U.S. were identified.[31-36] All but one case[32] of CRS were born to women who had been born outside of the U.S. and either traveled internationally or lived outside of the U.S. during pregnancy. We therefore consider foreign birth, recent immigration to the U.S., and international travel as risk factors for CRS.

Rubella Seroprevalence

Immunization from rubella via vaccination or infection results in the production of virus-specific IgG antibodies, which persist in an immunized individual's serum for decades.[37] Serological assays such as ELISA are useful for directly measuring susceptibility to rubella by quantifying the concentration of rubella antibodies in an individual's blood. These quantities can be used to calculate the proportion susceptible when applied at the population level, giving a sense of the magnitude of infection risk experienced in the population of interest. Furthermore, the study of population-level immunity can be used to identify socio-demographic groups with comparatively lower levels of immunity.[38] Several studies have estimated the prevalence of rubella susceptibility in the U.S. over time, but few have been conducted since the virus was eliminated and fewer still have estimated the proportion susceptible among women of reproductive age specifically. In general, the published literature does not consider socio-demographic factors associated with travel for men and women separately and may mask

meaningful susceptibility differences within socio-demographic groups if these differences vary by sex. To our knowledge, no studies have estimated differences in seroprevalence among demographic groups considered likely to travel during pregnancy.

Two studies have assessed seroprevalence of rubella antibodies among pregnant women. Bascom et al.[39] assessed performance on recommended practices surrounding perinatal hepatitis B and rubella prevention at 25 hospitals located in New Hampshire. The authors evaluated rates of prenatal screening, patient seroprevalence, and the administration of vaccine before hospital discharge for rubella to non-immune women who delivered at the included hospitals. Records from patients delivering infants in 2000 (n=2,021) were included in the analysis. The precise age range for patients was not reported but was theoretically between 10 and 54 years; 57% of patients were in the age range of 25-34 years. Among (n=2,008) women screened for rubella immunity, 6.7% were found susceptible. Susceptibility did not differ significantly by age, gravidity, nor parity in univariate analyses. However, interpretation of results from this study is difficult, as the laboratory methods used to measure antibody concentrations for rubella were not described in the patient record and were not presented in the publication. Immunity to rubella was assessed by the authors according to hand-written notes in the medical record categorizing lab results as immune, non-immune, or equivocal. Without knowledge of the antibody thresholds used to determine susceptibility, the ability to draw comparisons between this and other studies is limited. Moreover, the investigators did not consider patient characteristics other than age, parity, and gravidity as predictors for susceptibility; as such, few inferences can be made about susceptibility among women expected to travel. Finally, as the authors indicate, overall prevalence of rubella

susceptibility among women in this study may not reflect prevalence of U.S. women overall, as foreign born women are expected to have higher levels of susceptibility than women born domestically, and the population of foreign-born women in New Hampshire is relatively small compared to that in the U.S. as a whole.[39]

Kennedy et al.[40] evaluated antibody titers to rubella in their survey of serum samples from pregnant women in Iowa in order to test whether rubella immunity predicts mumps immunity. Serum samples (n=900) collected from pregnant women for routine antenatal screening between January and November 2004 were selected from those stored at the Iowa State Hygienic Laboratory. Immunity to rubella was assessed via a commercially available rubella IgG ELISA. Among the 785 samples for which women's ages were known, average age was 28 years (range 14 to 44). The cutoff used to determine immunity was not described. Though the investigators estimated seroprevalence to rubella among a large sample of pregnant women falling within the age range typically considered reproductive, the study was not able to determine differences in susceptibility by socio-demographic characteristics, as data on characteristics other than age were not available to the investigators. Further limitations as they relate to our purposes were use of a sample specific to Iowa, whose demographic makeup may vary considerably from the total U.S. population and failure to report the threshold used to determine rubella immunity.

A third study,[41] also conducted in Iowa, evaluated susceptibility among women receiving prenatal care at a high-risk clinic in 2007. Serologic screening results from 641 women were included in the analysis, among whom 44 (6.9%) were found seronegative. The specific age range of the sample was not provided, but when grouping women by age

categories defined as <20, 20-29, and ≥30, seronegativity to rubella was 10.2%, 6.2%, and 5.9%,respectively. Susceptibility was highest among Native Americans (17.3%), followed by white (7.3%), Black (5.9%), and Hispanic (4.6%) groups. In a univariate analysis and multivariate analysis adjusting for age, the difference between white and Native American groups was significant. The authors indicated that susceptibility to rubella may differ by age and race, but as statistical evaluations were reported for only race-ethnicity comparison, inferences about susceptibility by age or between other racial and ethnic groups cannot be made. In addition, individuals reporting Asian race or Somalian nationality were excluded from the study as well as those who identified as "other" race or ethnicity.

In the only study emphasizing the risk of acquiring rubella during international travel, Rosario-Rosario et al.[42] estimated seroprevalence of rubella by birth cohort in the Lehigh Valley Region using serum samples from individuals born prior to 1996. The goal of the study was to identify differences in susceptibility by age in order to identify groups at greatest risk of infection during travel. Samples were obtained from leftover outpatient serum samples taken between November 2013 and February 2014 at the Lehigh Valley Health Network. Antibodies to rubella were assessed using a commercially available enzyme immunoassay. The determination of immunity was made at a threshold of ≥10 IU/mL. Participants with equivocal results (5-9 IU/mL) were excluded from the analysis. The authors found no significant differences by sex. When grouping the study sample into 10-year age cohorts starting with birth in the year 1957, a pattern of decreasing immunity with age was observed over the birth cohorts spanning the years 1967 to 1995

and increasing immunity with age over the remaining birth cohort groups. However, differences in immunity between cohorts were not significant.

Four rubella seroprevalence studies utilizing data from the National Health and Nutrition Examination Survey (NHANES), a survey enrolling a nationally representative sample of US residents, have been published since 2000. One study[43] evaluated rubella seropositivity among participants from NHANES III, conducted from 1988 to 1994. Women of reproductive age in this study are not expected to be representative of women currently of reproductive age because rubella vaccination rates changed substantially during the 1990s,[1] and rubella was eliminated from the U.S. in 2004. Accordingly, we did not review this study further.

The remaining NHANES studies evaluated seroprevalence using an immunity threshold of $\geq$10 IU/mL, determined using an enzyme immunoassay. The second study was a report published by the National Center for Health Statistics.[44] In this report, seroprevalence to rubella and other infectious diseases were estimated among NHANES respondents aged 6-49 years participating in the survey between 1999 and 2004. The authors compared data from Los Angeles county residents to that from the NHANES sample overall, finding that rubella seropositivity was approximately 91% in both groups; this finding was consistent across Mexican American respondents in both groups as well. Other socio-demographic variables were not considered.

In a third study using NHANES data, Hyde et al.[45] estimated seroprevalence of rubella antibodies, comparing these estimates across two time periods (1988-1994, 1999-2004) in order to assess changes in seropositivity within demographic groups of interest and to evaluate whether immunity to rubella in the 1999-2004 survey exceeded the

elimination threshold of 87%. Separate analyses were carried out evaluating rubella susceptibility among school-age children (6-19 years) and adults of reproductive age (20-49 years). The authors found that seropositivity for rubella was 91.5% among female NHANES 1999-2004 respondents.

Lebo et al.[46] conducted the most recent study estimating seroprevalence of antibodies to rubella using NHANES data. Using data from NHANES 2009-2010 for respondents aged 6-49 years, the authors estimated overall prevalence of rubella seropositivity and in several socio-demographic groups. Seropositivity was defined as rubella IgG ELISA II result of >10 IU/mL. Respondents in older age categories had significantly lower prevalence of rubella immunity than those aged 6-11 years. In reproductive aged groups, seropositivity was 96, 93, and 94% among participants aged 20-29, 30-39, and 40-49 years, respectively. Female participants had significantly higher seroprevalence than men, and non-Hispanic black participants had significantly higher seroprevalence than white participants. No significant differences were found between Mexican Americans and white participants or between groups defined by U.S. and non-U.S. place of birth. Using a large (n=5,054), nationally representative sample, this study provides evidence of differences in seroprevalence of rubella antibodies by age, sex, and ethnicity. However, differences by age and ethnicity were not evaluated by sex and susceptibility was, accordingly, not assessed by socio-demographic characteristics among women of reproductive age.

Two studies estimated seroprevalence of rubella among military recruits. Eick et al.[47] assessed immunity among a cohort of recruits enlisting in the U.S. Air Force, Army, Navy, or Marine Corps between January 2000 and December 2004. Demographic,

occupational, immunization, and medical data on recruits aged 17 to 35 years were extracted from the Defense Medical Surveillance System. The analysis included data from 3,000 subjects with serum specimens available for laboratory testing, which were selected to reflect the distribution of demographic characteristics among recruits to the U.S. military. Immunity to rubella was quantified using the Rubella Captia IgG ELISA, measuring an Immune Status Ratio (specimen optical density/calibrator optical density). Cutoff values for negative, equivocal, and positive results were $\leq$ 0.90, 0.91-1.09, and $\geq$1.10, respectively. Equivocal results were considered negative for the purposes of analysis. Seronegativity was estimated at 5.2% in the sample overall, and 5.4% among females specifically. Odds of seropositivity were higher among recruits aged 30-35 as compared to those aged 17-19 years. White recruits had the lowest rates of seropositivity (93.3%), and seropositivity was significantly higher among black, Hispanic, and "other" race/ethnicity groups. In a subsample of the population that underwent targeted vaccination following sample collection, foreign-born recruits had higher odds of seropositivity than did U.S.-born recruits. Seropositivity did not vary significantly by education in years or by location of birth among the subsample that was subsequently universally vaccinated. This study provides evidence that immunity to rubella may differ by age, ethnicity, and place of birth, with white and foreign-born individuals more likely to be susceptible to infection, and older individuals more likely immune. The study sample fell within the range of reproductive age, though individuals aged 36 and older were not included. The finding that 5.6% of females are susceptible to rubella may not apply to the overall population of reproductive-aged women in the U.S. Furthermore, results may not apply on the national scale as the study included a group of military

recruits, which may comprise a specific, non-representative segment of the U.S. population.

The second study including a sample of military recruits was performed by Lewis et al.[48] The authors estimated seroprevalence in the total population of recruits and in groups categorized by age and sex using antibody titer data from all recruits to the U.S. Air Force who entered basic training between April 25, 2013 and April 24, 2014. The goal of the study was to determine whether seroprevalence of antibodies to measles, mumps, and rubella surpassed herd immunity thresholds. Rubella titers were estimated using the BioRad BioPlex 2200 MMRV IgG multiplex flow immunoassay, which allowed for the simultaneous measurements of antibodies to measles, mumps, and rubella. The titer threshold used to determine seropositivity was not reported. Among the sample overall (n = 32,502), rubella seroprevalence was 82%. Among females, this proportion was 86%, and was significantly higher than that observed among males, after adjusting for differences in age (OR 1.06, $p = 0.007$). Rubella varied from 81.6% in the age group 20-24 years to 86.5% in the age group 30-34 years. Prevalence of rubella immunity was significantly higher among recruits aged 30-34 (OR 1.05, 95%, $p < 0.001$) than those aged 17-19. This study demonstrates a small variation in rubella seropositivity by age among a population of military recruits. Though the study sample was likely of reproductive age, the upper bound for recruits was not provided. Like the study by Eick et al., the results from this study may not apply to the U.S. population of reproductive age if military recruits differ systematically from the U.S. population in terms of characteristics that predict rubella immunity.

Finally, Crooke et al.[49] conducted a seroprevalence study to estimate population level immunity to rubella in Olmsted, MN and its surrounding municipalities. Immunity to rubella was measured for the overall study sample and within groups characterized by sex, age, and BMI quartile. Approximately 1,400 Mayo Clinic Biobank samples from participants aged between 20 and 44 years were included for analysis. IgG antibody titers to rubella virus were estimated using the Zeus Rubella IgG ELISA test. Individuals with titers $\geq$ 10 IU/mL were considered rubella immune, while those between 8.19 and 9.99 IU/mL were equivocal, and those below 8.19 IU/mL were considered susceptible. Dates of sample collection were not provided, but began in 2009.[50] The biobank participants had a median age of 36.82 years (IQR: 32.55-40.81); 80.2% were female. Susceptibility to rubella was 2.2% in the sample overall, and women had a higher average titer to rubella than men. For the purposes of understanding differences in susceptibility to rubella among demographic groups, a weakness of this study is that it compared average titers between groups, rather than comparing the proportions considered immune. In addition, though the study included individuals who fell within the reproductive ages, the ages of participants did not span this category, which is defined by the WHO as ages 15-49.[51] With a mean age of about 37 years, participants were also older on average than the average reproductive age in the U.S.[52] and a substantial portion would have been born prior to the introduction of RCVs, potentially making this sample a poor reflection of immunity among reproductive age women in the U.S. more recently.

Objectives

A woman's chances of acquiring rubella infection and subsequently birthing an infant affected by CRS depends on both her rubella immunity status and her exposure to

the rubella virus during pregnancy. Seroprevalence studies conducted shortly before or following rubella's elimination from the U.S. indicate that immunity to the rubella virus may be related to age, foreign birth, race, and ethnicity,[42,42,46-48] while case reports and surveillance data published in the post-elimination era suggest that rubella and CRS are associated with travel, foreign birth, and recent U.S. immigration.[31,33-36] In order to identify groups at highest risk for CRS on a national scale, we evaluated the hypotheses that susceptibility to rubella is associated with age, foreign birth, race-ethnicity, foreign travel, and recent U.S. immigration. We defined susceptibility to rubella as an IgG titer below 10 IU/mL, as defined in several previous seroprevalence studies.

As previously stated, a majority of CRS cases occurring in the U.S. over the past 15 years have been born to mothers who recently traveled to or immigrated from foreign countries and endemic rubella transmission is known to continue in countries outside of the Americas. In the absence of travel advisories provided by health agencies such as WHO and CDC, women may unknowingly travel to areas with a high prevalence of rubella. Accordingly, a second objective was to identify countries where risk of rubella infection and CRS are the highest in order to highlight areas to which travel may be inadvisable during early pregnancy. We used a rubella transmission model, informed by previous work on rubella dynamics, to calculate the country-specific force of infection, defined as the rate at which susceptible individuals are infected, as a measure of rubella and CRS risk.

Methods

The National Health and Nutrition Examination Survey

The source of data for this study was the National Health and Nutrition Examination Survey (NHANES), a series of cross-sectional surveys designed by the National Center for Health Statistics (NCHS) to assess the health and nutrition status of the U.S. population.[52] The survey employs a stratified, multistage, probability-cluster design to generate a representative sample of the country's civilian noninstitutionalized residents.[52] Consecutive NHANES surveys are conducted in 2-year cycles, with approximately 5,000 people enrolled each year.[52] In the 2009-2010 cycle, Hispanic and non-Hispanic black persons, low-income persons of non-Hispanic or "other" race, and adults aged 80 and over were oversampled to allow for precise health indicator estimates within these groups.[4] Respondents answered a household interview that included demographic and household information and were asked to participate in an examination which involved assessment of several health measures as well as collection of blood and urine specimens for laboratory testing. The Institutional Review Board of the NCHS approved the study protocol.

a. Laboratory Analysis

Serum samples collected from NHANES 2009-2010 respondents who participated in the exam portion of the study were tested for IgG antibodies to rubella using the Wampole Rubella IgG II ELISA. The laboratory assay procedures are described elsewhere.[53] We defined non-immunity to rubella as <10 IU/mL based on the CDC's recommendation that individuals with titers below this threshold be immunized regardless of their vaccination history.[54] However, since serologic correlates of immunity

to rubella are not well understood, we also conducted a secondary analysis in which rubella susceptibility was defined as a titer at or below 8.18 IU/mL, as titers between 8.18 and 10 IU/mL are considered equivocal for rubella immunity.[53] The results of this analysis are displayed in the supplement (Tables S1 and S2).

b. Statistical Analysis

We calculated prevalence of susceptibility to rubella in the participant sample overall and in several socio-demographic groups. Using univariate logistic regression models, we assessed the relative difference in odds of non-immunity comparing groups hypothesized to be at risk for CRS to those thought to be at lower risk. Regressions were performed for each of the following variables: age, race/ethnicity, birth outside the U.S., citizenship status, reported receipt of hepatitis A vaccine, and having lived in the U.S. for less than 10 years. All prevalence estimates and odds ratios were weighted to represent the U.S. civilian non-institutionalized population, accounting for NHANES oversampling and non-response to the household interview or physical exam.[55] Standard errors were calculated using the Taylor series linearization method available through Stata version 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Adult female participants of reproductive age (18-49 years) with rubella IgG laboratory results were included in the analysis. Demographic variables were collected during the household interview portion of the survey. Race and ethnicity were coded as non-Hispanic white, non-Hispanic Black, Hispanic, and other non-Hispanic. Hispanic ethnicity included women who reported being Mexican American or other Hispanic. Other, non-Hispanic race-ethnicity included women who reported non-Hispanic ethnicity

and race other than Black or white, including mixed race. Country of birth was coded as birth in the U.S. and birth outside of the U.S. Citizenship status was categorized as citizen, non-citizen, or don't know/refused. Questions regarding international travel were not asked of NHANES participants. To assess the association between travel and rubella susceptibility, we performed a logistic regression categorizing individuals based on reported receipt of vaccination for hepatitis A, since travel is one indication for the vaccine in the U.S. Hepatitis A vaccination was assessed during the participant exam. Women who reported receiving at least one dose of the vaccine were categorized as such while those who stated they had not been vaccinated or were not sure were categorized as not reporting vaccination.

Participants who reported being born outside of the U.S. during the household questionnaire were asked a follow-up question regarding how long they have lived in the U.S. We hypothesized that individuals living in the U.S. for shorter periods have higher prevalence of susceptibility than individuals living in the U.S. for longer periods. To test this hypothesis, we conducted a subgroup analysis using logistic regression comparing women who had resided in the U.S. less than 10 years to those who lived in the U.S. 10 years or more. Individuals who refused to answer or who reported not knowing how long they had lived in the U.S. were re-coded as missing and excluded from the sub analysis.

Country-Specific Rubella Risk

We used a discrete-time deterministic age-structured compartmental rubella transmission model to calculate country-specific estimates of risk for rubella infection, building from previous work describing rubella dynamics.[56,57] This model defined transitions at each time step from every combination of epidemiologic compartment (i.e.,

maternally immune, susceptible, infected, recovered, and vaccinated) and age group (grouped into one month intervals up to 20 years old and 1 year intervals from 20 to 100 years old) to every other possible combination of epidemiological stage and age group.

We simulated rubella dynamics for all WHO member countries from 1980 to 2020, with the exception of countries in the WHO Americas Region where rubella has been eliminated. Demographic parameters including population size, crude birth rates, and age-specific death rates were extracted from the United Nations Population Division estimates via the *wpp2017* package. Routine and campaign associated rubella vaccination coverage were time- and country-specific; they were extracted from the WHO/UNICEF estimates of national immunization coverage from 1980 to 2020.[58] Vaccination coverage was adjusted based on the assumptions that repeated vaccination activities are not completely independent and a portion of the population may always remain inaccessible to vaccination. Duration of maternal immunity and vaccine efficacy were assumed from published literature and are constant across time and country.

The model output was annual age-specific force of infection. The country average force of infection was estimated by taking a weighted average of the age-specific estimates. We combined these estimates for each country, with country-specific travel data to calculate both risk of acquiring rubella infection and the expected number of infections among travelers each year, assuming an average travel duration of 2 weeks. Annual travel volume between the United States and other countries was estimated as the mean annual travel from 2017-2019, using full itinerary travel volume data from OAG (https://www.oag.com/). Risk for infection for each country was calculated as the annual force of infection per 1,000 susceptible, multiplied by the number of annual travelers to

the country. Relative risk of infection was estimated as the country-specific risk divided by the mean risk for all countries included in the analysis. The expected number of infections was the number of annual travelers expected to be susceptible multiplied by the force of infection for a two-week period. Expectation of susceptibility (3%) was derived from our preceding analysis of NHANES serology data. Countries included in the analysis were located in any of the 5 WHO regions that have not yet eliminated rubella and with estimates available for both force of infection and annual travel.

Results

NHANES Results

Participant Characteristics

Of the 1,836 female NHANES 2009-10 participants aged 18-49 years, 1,800 completed both the household interview and the physical exam. Among these women, 1,685 had lab results for IgG antibodies to rubella. Women excluded from the analysis based on absence of exam or rubella IgG data did not differ from women included on any variables in our analysis.

Table 1 shows characteristics of the analytic sample by rubella susceptibility, weighted to represent the population of adult U.S. women of reproductive age. Overall, 54 (3.3%, 95% CI: 2.3-4.7%) participants were seronegative for rubella. Susceptible participants were on average older than those who were immune, and were more likely to report white race, Hispanic ethnicity, and U.S. citizenship. In contrast, women who were rubella immune were more likely to report Black or other race, to be born outside the U.S. and receive at least one dose of hepatitis A vaccine.

Rubella Susceptibility

Table 2 shows the weighted prevalence of susceptibility to rubella within categories of socio-demographic variables, as well as univariable odds ratios estimating relative differences in susceptibility between comparison and referent groups for each variable. Distributions of rubella IgG antibodies by categories of each variable are displayed in figures 1-6.

The proportion susceptible to rubella within 5-year age categories ranged from 0.82% for ages 18-19, to 7.24% for ages 40-44 years. Women aged 25-29 were selected as the referent group, as this age group had the highest rate of fertility in the U.S. during the study period.[59] There were no significant differences between the referent and other age groups except that women aged 40-44 had a significantly higher odds of susceptibility.

Susceptibility ranged from 0.86 to 4.04% among racial and ethnic groups, with the lowest proportion occurring in the group categorized as "other" (0.39%) and the highest proportion susceptible occurring among the group identifying as Hispanic (4.15%). White women were chosen as the referent group in our regression analysis. Odds ratios comparing Black (OR 0.59, 95% CI 0.22-1.60) and Hispanic (OR 1.12, 95% CI 0.55-2.27) racial groups to the referent group did not differ significantly. Women reporting other race had significantly lower odds of susceptibility as compared to white women (OR 0.10, 95% CI 0.01-0.85).

For the variable defined as birth outside of the U.S., 3.52% and 2.49% of individuals were susceptible in the U.S.-born and foreign-born groups respectively; the relative odds of susceptibility comparing women born in the U.S. to those born elsewhere was not significant (OR 0.70, 95% CI 0.25-1.99). Similarly, odds of rubella susceptibility were not different between categories of citizenship status. The odds ratio comparing non-citizens to citizens was 0.53 (95% CI 0.20-1.35), while it was 2.36 (95% CI 0.20-27.89) for women who refused to answer or did not know their citizenship status compared to citizens.

The proportion of susceptible individuals among women who reported receipt of at least one dose of hepatitis A vaccine was 3.85%, while it was 2.01% for those not reporting hepatitis A vaccination. Odds of susceptibility were not significantly different between the two groups (OR 0.51, 95% CI 0.23-1.22).

Of 478 participants who reported being foreign-born, 441 provided data on number of years living in the U.S. Within this group, susceptibility to rubella was 3.31% overall. For the 274 participants who had lived in the U.S. for at least 10 years and the 167 who had lived in the U.S. for 9 years or fewer, the respective prevalence of rubella susceptibility was 2.55% and 1.20% . The odds ratio of susceptibility (OR 0.46, 95% CI 0.09-2.25) was not significantly different for the two groups. A multivariable analysis adjusting for differences in age between the two groups yielded similar insignificant results (OR 0.74, 95% CI 0.14-3.81).

Transmission Model Results

We estimated the force of rubella infection for 147 countries. Of these, only one country (Yemen) had no travel data available. Tables 3 and 4 display the 20 countries with the highest force of infection per 1,000 (FOI) and highest relative risks of infection, respectively. Country specific FOI estimates ranged from <0.001 to 85.3, with the highest estimated FOIs in countries in Africa. Forty-three countries had annual forces of infection estimated above one infection per 1,000 susceptible population. Among these countries, the median FOI was 57 infections (IQR 38-73).

The median FOI was below 0.001 in each of the 5 WHO regions. However, the distributions of FOI varied substantially between regions (Figure 7). The African region (AFR) had the highest mean FOI at 26.3 (75^{th} percentile: 70.9), and 16 (35%) of its 45

countries had FOIs above one. In the Eastern Mediterranean region (EMR) the mean FOI was 22.7 (75^{th} percentile: 50.1), while in the European region (EUR), it was estimated to be 7.7 (75^{th} percentile: 0.05). Mean FOI was estimated for the Western Pacific (WPR) at 7.6 (75^{th} percentile: 0.001) and for the Southeast Asia (SEAR) region at 6.5 (75^{th} percentile: 3.4). In each respective regions EMR, EUR, WPR, and SEAR the percentage of countries with FOIs of at least one was 24, 38, 19, and 27%.

Ordering of countries in terms of risk for rubella acquisition varied from the ordering based on FOI alone when accounting for volume of U.S. travel specific to each country. Travel from the U.S. to all countries totaled approximately 50 million trips, and the bulk of this travel was to EUR (56%) and WPR (29%). As such, countries located within these WHO regions were more heavily represented among countries with the highest probabilities of infection for U.S. travelers (Table 4; Figure 8). The expected annual number of infections among U.S. trips per country each year ranged from <0.001 to 148, with 23 (16%) of included countries expecting at least 1 infection per year. However, when examining FOI by travel volume (Figure 9) there appears to be a trend of decreasing FOI with increasing travel, potentially indicating that travel to countries with the highest forces of infection is rare compared to countries with lower FOIs.

Discussion

This study evaluated susceptibility to rubella among women of reproductive age in the time following elimination of endemic transmission of rubella in the U.S. Using an analysis of serological and survey data among the U.S. population, we found significant differences in rubella seroprevalence between women aged 40-44 years as compared to women aged 25-29, and between white women as compared to women reporting "other" non-Hispanic race-ethnicity. No other significant differences were observed comparing women expected to have higher rubella seroprevalence (via vaccination or natural infection) to those hypothesized to have lower rubella seroprevalence. In addition to our analysis of rubella seroprevalence by socio-demographic characteristics, we assessed the risk of infection for various countries using country-specific estimates of the annual force of infection derived from a rubella transmission model. We found that the rate of infection during a two-week travel period, given susceptibility, is high in several countries.

On the national scale, this study suggests no particular risk factor that can be used for targeting clinical recommendations surrounding travel during pregnancy as they relate to rubella. This finding may be due to an absence of differences between socio-demographic groups in the U.S., but may also be explained by other factors. The sample size of several groups in our study may not have been sufficient for detecting true differences in rubella non-immunity among these groups; seronegativity to rubella also was rare. In addition, the sampling strategy employed by the NHANES survey may not have captured groups at high risk for rubella susceptibility, such as unvaccinated refugees or religious and cultural groups that abstain from vaccination. Another possibility is that the data collected through NHANES were not granular enough to be able to identify

specific groups with higher proportions susceptible. For example, rubella immunity may vary by country of birth, but this data was available in four broad categories rather than by specific country. Furthermore, national level data may have masked heterogeneity in rubella susceptibility at smaller spatial scales.

Despite the lack of risk factors for rubella seroprevalence, our finding that approximately 3% of adult female U.S. residents of reproductive age are susceptible to rubella may be clinically important. Three percent of the female population of reproductive ages represents a substantial number of women (~ 2 million, and about 120,000 women giving birth each year)[60] potentially at risk for CRS, as women of reproductive age in the U.S. comprise a population of approximately 68 million.[61] Based on this knowledge, we are not calling for a recommended end for travel to rubella endemic areas during pregnancy among women found susceptible, but rather are highlighting the need for discussions of risks associated with travel, and perhaps a recommendation of delaying travel until later in pregnancy, when risk of CRS is lower.

Our analysis suggests that travel to areas with the highest forces of infection is relatively rare, as countries with the highest forces of infection are not necessarily those where the highest number of rubella cases are expected to occur (see Tables 3 and 4, Figure 10). This observation indicates that there is likely only a small proportion of U.S.-resident women who are at considerable risk for prenatal rubella infection. In addition, countries with the highest forces of rubella infection are located in regions where rubella vaccination rates are low or rubella vaccine has not been introduced into the childhood immunization schedule,[19] meaning women who were born in these countries before immigrating to the U.S. may not have been vaccinated nor infected, depending on the age

at which they emigrated. These women may represent a group at particularly high risk, as they may also be more likely to return to their countries of birth for purposes such as visiting family members.[62]

This study had several limitations. Participants in the NHANES survey were aged 18-49 years in 2009-2010. The two older age groups were born prior to or shortly following the licensing of rubella vaccine in the U.S., and as such, their levels of susceptibility may not be representative of women in these age ranges today. More specifically, women in the age category 40-44 years had lower immunity than other age groups, which may be an artifact of the implementation of the rubella vaccine rollout since this group may have been less likely to be vaccinated than younger age groups, but also less likely than the oldest age group to have acquired natural immunity through infection. Moreover, vaccination rates may also differ between the current time period and 2009-2010. However, because NHANES no longer collected rubella antibody data following its 2009-2010 cycle, more recent data could not be collected from this source.

Travel is associated with risk for CRS as most cases occurring in the past 15 years have occurred subsequent to travel or immigration from a foreign country. It is therefore important to measure prevalence of susceptibility among demographic groups expected to travel, especially among those who are expected to travel to countries with endemic rubella transmission. We were not able to identify a direct measure of travel in the publicly available NHANES datasets, and used hepatitis A vaccination status as its proxy, since travel is one indication for the vaccine. However, it is also possible that this vaccine is more commonly administered to those who travel and are from higher SES groups, or who otherwise have better access to healthcare and are thus more likely to have been

adequately vaccinated against rubella. Our finding that individuals who were vaccinated from hepatitis A had a higher seroprevalence of rubella supports this hypothesis.

Our analysis of country-level risk for rubella infection had several limitations as well. The force of infection assumes that the proportion of infectious individuals in a country overall is equal to the proportion of infectious individuals with whom a traveler comes into contact, and that the probability of infection is constant across all contacts with infectives. These assumptions may be violated if social mixing is not uniform across susceptible and immune travelers, or if infection probabilities per contact vary across these groups as well. For example, susceptible women may travel to visit family members living in the country and share closer quarters with infectious individuals, while immune individuals may be more likely to travel for business or leisure purposes and only come into contact with infectives in public. By applying the proportion susceptible to rubella for the U.S. overall to our estimates of expected infections per country, we assume that the probability of travel is equal among susceptible and immune individuals and that the ratio of susceptible to immune travelers does not vary by country. However, this assumption may not hold if immune status is related to likelihood of travel. For example, we may underestimate the expected number of infections acquired in a country if the proportion of travelers susceptible is higher than that observed in the U.S. population overall. Additionally, the transmission model used to estimate the force of infection for each country relies on potentially biased data to estimate epidemiological and demographic input parameters, and makes many assumptions about transmission patterns across the country that will likely bias results, but in unknown directions. For

example, the model does not allow for spatial demographic and epidemiologic heterogeneities and assumes homogenous spatial mixing across the entire country.

Based on the limitations of our study, future research may include larger numbers of participants in order to achieve adequate power for making assessments of national level data. In addition, research should focus on capturing some granularity in socio-demographic measures that is missed by NHANES. Seroprevalence studies conducted at smaller spatial scales (e.g., counties, cities, hospitals) may detect important differences in susceptibility based on the particular demographic makeup of the target population that can be used to make local travel recommendations.

Conclusion

We provide evidence that approximately 3% of the population of reproductive aged women in the U.S. are susceptible to rubella, translating to roughly 2 million women potentially at risk. The force of infection in some rubella endemic countries remains high, and as such, women expected to travel to endemic areas comprise a group that may be at especially high risk for infection. Though rubella and CRS are rare in the U.S. overall, risk should be reduced to the furthest extent possible given that consequences of maternal infection during pregnancy can be severely damaging to the fetus. The finding that a large number of women of reproductive age are potentially susceptible to infection indicates a role for a revision of travel guidelines to help reduce individual-level risk for CRS. On the basis of the high probability of infection estimated for countries with endemic rubella transmission, future research should focus on identifying groups most likely to be rubella susceptible and likely to travel to areas with ongoing transmission.

Tables and Figures

Table 1. Participant characteristics, by rubella susceptibility (IgG <10 IU/mL)

Characteristic	Susceptible		Immune	
	N[a]	Proportion ± SE (%)[b]	N[a]	Proportion ± SE (%)[b]
Overall (N)	54	3.3 ± 0.56	1631	96.7 ± 0.56
Age (years)				
18-19	2	1.3 ± 0.9	124	5.3 ± 0.7
20-24	7	17.3 ± 8.3	255	14.5 ± 1.0
25-29	6	8.9 ± 4.7	242	16.2 ± 0.9
30-34	6	10.8 ± 3.9	240	14.8 ± 1.2
35-39	8	10.5 ± 4.0	242	15.5 ± 1.2
40-44	19	39.5 ± 6.4	265	17.3 ± 1.1
45-49	6	11.7 ± 5.2	263	16.4 ± 1.5
Race/ethnicity				
White	25	68.5 ± 9.2	706	60.5 ± 4.1
Black	6	9.0 ± 4.0	288	13.4 ± 1.1
Hispanic	22	21.5 ± 8.6	522	17.1 ± 3.1
Other	1	1.0 ± 1.0	115	9.0 ± 1.4
Born outside of the US	11	15.3 ± 6.1	467	20.5 ± 2.6
Citizenship status				
Citizen	46	92.4 ± 3.2	1325	87.5 ± 1.9
Not a citizen	7	6.8 ± 3.1	301	12.2 ± 1.9
Refused/Unknown	1	0.8 ± 0.8	5	0.3 ± 0.2
Received hepatitis A vaccine	12	17.6 ± 6.3	518	29.5 ± 1.5

Abbreviations: SE, standard error.
a. N: unweighted number of respondents.
b. Weighted proportion: Proportion of respondents, weighted to account for oversampling and non-response.

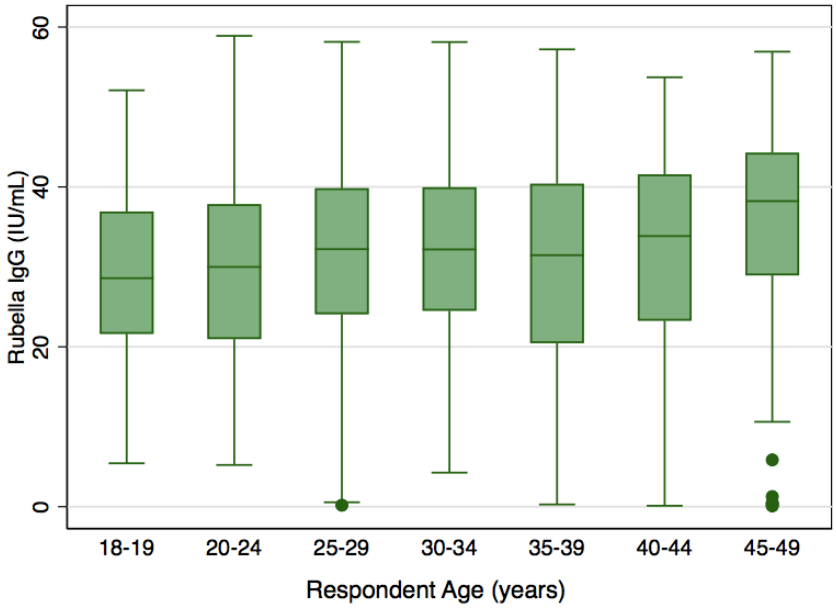
Table 2. Prevalence and univariable odds ratios of rubella susceptibility (IgG <10 IU/mL) among female NHANES participants, aged 18-49 years

Characteristic	Participants (N)	Prevalence ± SE (%) [a]	OR (95% CI) [a]
Age group, years			
18-19	126	0.82 ± 0.62	0.43 (0.07-2.73)
20-24	262	3.94 ± 1.97	2.18 (0.33-14.57)
25-29	248	1.85 ± 0.90	Ref
30-34	246	2.45 ± 0.90	1.33 (0.36-4.89)
35-39	250	2.28 ± 1.05	1.24 (0.24-6.38)
40-44	284	7.24 ± 1.86	4.14 (1.11-15.52)[b]
45-49	269	2.39 ± 1.15	1.3 (0.30-5.59)
Race/ethnicity			
White	731	3.73 ± 0.86	Ref
Black	294	2.24 ± 0.85	0.59 (0.22-1.60)
Hispanic	544	4.15 ± 1.01	1.12 (0.55-2.27)
Other	116	0.39 ± 0.39	0.1 (0.01-0.85) [b]
Country of birth			
U.S.	1207	3.52 ± 0.62	Ref
Outside of the U.S.	478	2.49 ± 1.13	0.70 (0.25-1.99)
Citizenship status			
Citizen	1371	3.50 ± 0.62	Ref
Not a citizen	308	1.87 ± 0.76	0.53 (0.20-1.35)
Refused/Unknown	6	7.87 ± 8.32	2.36 (0.20-27.89)
Received hepatitis A vaccine			
No	1155	3.85 ± 0.69	Ref
Yes	530	2.01 ± 0.76	0.51 (0.23-1.22)

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; Ref, reference group.

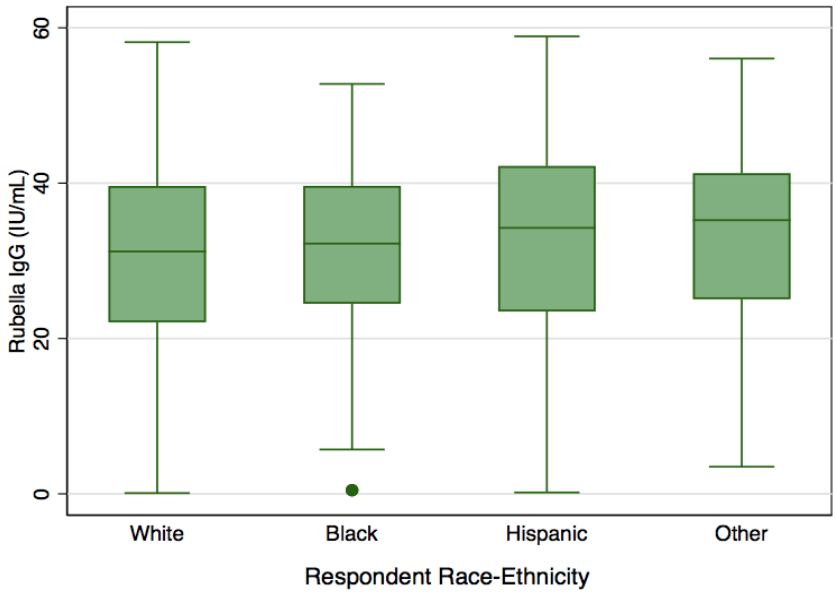
a. NHANES survey weights applied to represent the total U.S. noninstitutionalized population. Accounts for oversampling and non-response.
b. Indicates statistical significance.

Figure 1. Distribution of rubella IgG antibodies by age



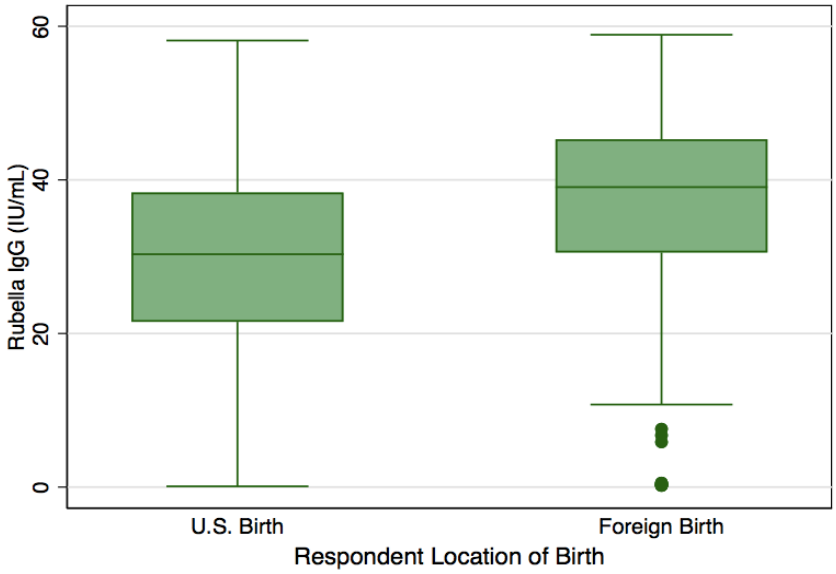
This figure displays the distribution of rubella IgG antibody concentrations by age among NHANES respondents. Respondents aged 40-44 years in 2009-2010 were found to have significantly higher odds of susceptibility to rubella as compared to those aged 25-29. However, the median rubella titer is generally similar across age groups, with a slight increasing trend in the median with increasing age.

Figure 2. Distribution of rubella IgG antibodies by race-ethnicity



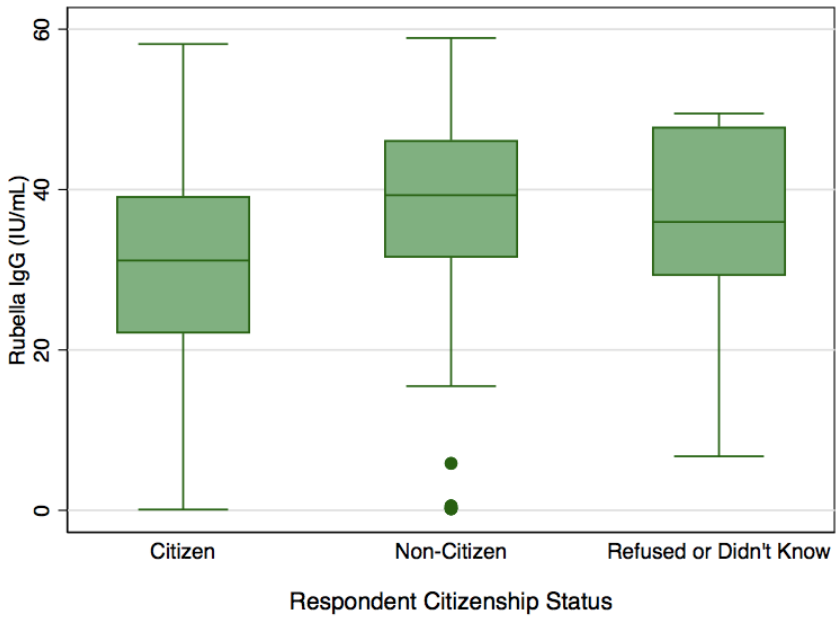
This figure displays the distribution of rubella IgG antibody concentrations across racial and ethnic groups reported by NHANES 2009-2010 respondents. In our weighted analysis, women reporting “other” race-ethnicity had lower odds of rubella susceptibility than women reporting white, non-Hispanic race-ethnicity (OR , 95% CI). Here, the full distribution of titers shows that the smallest variations in IgG titer occurred among individuals reporting Black, non-Hispanic race. Most titers are above the 10 IU/mL threshold for immunity, and the median titers is approximately equal across racial and ethnic groups.

Figure 3. Distribution of rubella IgG antibodies by location of birth.



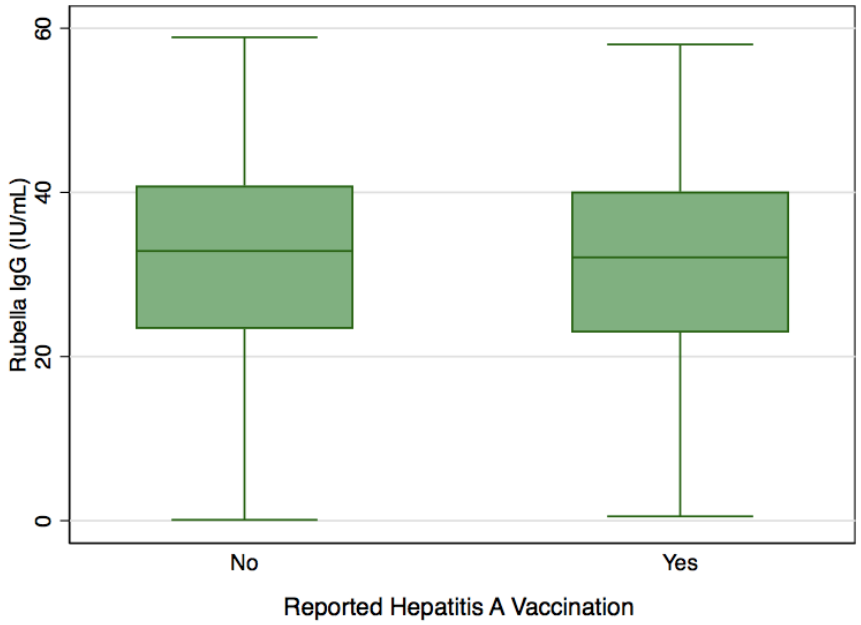
Foreign birth was considered a risk factor for rubella susceptibility, as the rubella vaccine is not available in all countries, and most CRS births in the U.S. since 2004 were to mothers born outside the U.S. This figure shows that among NHANES respondents, foreign-born women had higher IgG titers to rubella than women born in the U.S. Our analysis showed that women born in foreign countries had lower odds of susceptibility as compared to women in the U.S., however, odds did not vary significantly between the two groups. The higher titer observed among foreign born women could possibly be attributable to higher rates of natural infection, which is expected to induce a stronger antibody response as compared to vaccination.

Figure 4. Distribution of rubella IgG antibodies by citizenship status.



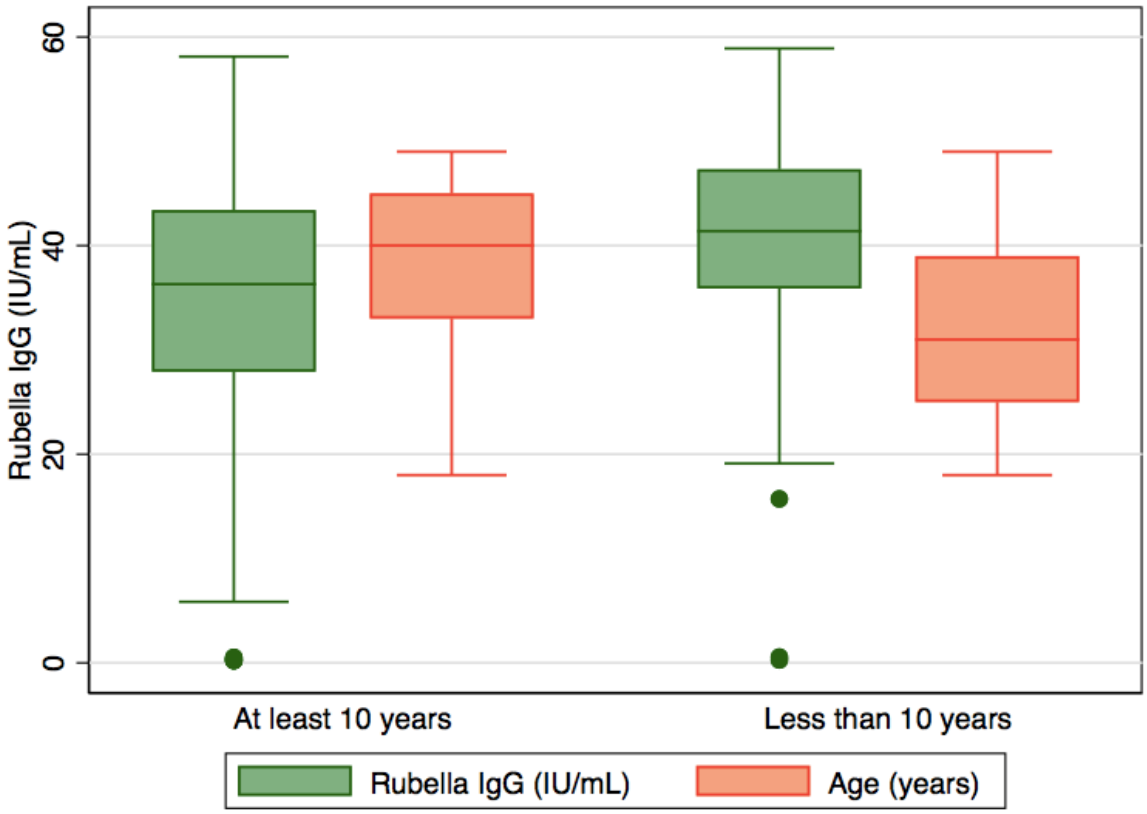
In NHANES 2009-2010, women who reported non-citizenship to the U.S. had lower odds of susceptibility than women who reported U.S. citizenship. Women who refused or did not know their citizenship status also had lower odds of susceptibility. Odds ratios for both comparisons were not significant. This figure shows the distributions of rubella IgG titers for each group. Median antibody titers are higher for the non-citizen and refused/did not know group. Similar to the observations made with respect to women born in the U.S. as compared to those born outside the U.S., women who are not citizens may have had higher rates of previous rubella infection and therefore mounted higher antibody responses.

Figure 5. Distribution of rubella IgG antibodies by reported receipt of hepatitis A vaccine.



We hypothesized that women reporting hepatitis A vaccination in NHANES 2009-2010 would have higher odds of susceptibility to rubella. Rubella A vaccination status was used as a proxy for travel, since foreign travel is on indication for the vaccine. However, odds of susceptibility were not significantly different between the two groups. This figure illustrates that the distributions of antibody titers are very similar between those who are vaccinated and those who are unvaccinated for hepatitis A.

Figure 6. Distribution of rubella IgG antibodies and age by length of time living in the U.S.



This figure shows the age and rubella antibody distributions for women who had lived in the U.S. for 10 years or more and those who had lived in the U.S. for less than 10 years. We hypothesized that immunity to rubella would be lower among women who had lived in the U.S. for a shorter duration, but found no significant differences in odds of susceptibility. Age distributions are displayed here to demonstrate whether differences in susceptibility by duration of U.S. residence may be driven by differences in age. As expected, women who have lived in the U.S. for at least 10 years are older than those who have lived in the U.S. for fewer than 10 years.

Table 3. Rubella risk estimates for twenty countries with highest estimated forces of infection

Country	WHO Region	No. Travelers	FOI[a]	Risk[b]	RR[c]	Expected Infections[d]
Niger	AFR	5,656	85.3	482.6	0.30	0.56
Guinea-Bissau	AFR	532	84.2	44.8	0.03	0.05
Guinea	AFR	12,122	81.7	990.7	0.61	1.14
Mali	AFR	7,981	81.4	649.7	0.40	0.75
Chad	AFR	4,627	80.9	374.5	0.23	0.43
Somalia	EMR	6,321	80.1	506.2	0.31	0.58
Democratic Republic of the Congo	AFR	15,173	79.7	1208.9	0.74	1.39
Central African Republic	AFR	1,878	75.6	142.0	0.09	0.16
Congo	AFR	4,040	75.3	304.0	0.19	0.35
Liberia	AFR	18,071	74.5	1345.7	0.83	1.55
Nigeria	AFR	285,900	73.9	21124.5	13.01	24.37
Equatorial Guinea	AFR	10,013	73.4	735.4	0.45	0.85
Comoros	AFR	275	71.0	19.5	0.01	0.02
Sudan	EMR	23,880	70.8	1691.4	1.04	1.95
Ethiopia	AFR	115,950	68.9	7993.0	4.92	9.22
Madagascar	AFR	6,667	67.5	450.0	0.28	0.52
Kyrgyzstan	EUR	20,917	63.5	1328.5	0.82	1.53
Iraq	EMR	64,787	63.3	4101.9	2.53	4.73
Afghanistan	EMR	24,979	63.3	1581.2	0.97	1.82
Georgia	EUR	39,416	58.6	2308.7	1.42	2.66

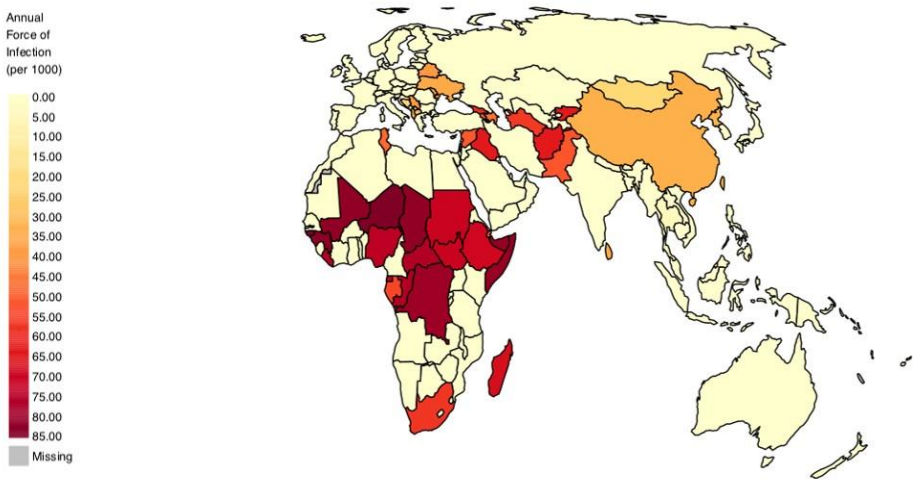
a. Annual force of infection per 1,000 susceptible, estimated from rubella transmission model.
b. Country-level risk for infection among all U.S. based travelers, equal to FOI * annual number of travelers.
c. Relative risk for infection, equal to country-specific risk/mean risk for all countries.
d. Expected infections among U.S. based travelers, equal to risk * proportion susceptible to rubella.

Table 4. Rubella risk estimates for twenty countries with highest relative risk of infection

Country	WHO Region	No. Travelers	FOI[a]	Risk[b]	RR[c]	Expected Infections[d]
China	WPR	3,861,091	0.03	128,594	79.20	148.38
Nigeria	AFR	285,900	0.07	21,124	13.01	24.37
South Africa	AFR	334,986	0.06	19,083	11.75	22.02
Pakistan	EMR	285,993	0.05	14,727	9.07	16.99
Ethiopia	AFR	115,950	0.07	7,993	4.92	9.22
Ukraine	EUR	213,962	0.03	7,311	4.50	8.44
Iraq	EMR	64,787	0.06	4,102	2.53	4.73
Serbia	EUR	87,130	0.04	3,340	2.06	3.85
Armenia	EUR	64,531	0.05	3,144	1.94	3.63
Albania	EUR	69,950	0.03	2,436	1.50	2.81
Georgia	EUR	39,416	0.06	2,309	1.42	2.66
Thailand	SEAR	623,315	0.00	2,106	1.30	2.43
Sri Lanka	SEAR	56,534	0.04	2,025	1.25	2.34
Sudan	EMR	23,880	0.07	1,691	1.04	1.95
Afghanistan	EMR	24,979	0.06	1,581	0.97	1.82
Belarus	EUR	35,057	0.04	1,371	0.84	1.58
Liberia	AFR	18,071	0.07	1,346	0.83	1.55
Kyrgyzstan	EUR	20,917	0.06	1,328	0.82	1.53
Tunisia	EMR	26,108	0.05	1,250	0.77	1.44
Democratic Republic of the Congo	AFR	15,173	0.08	1,209	0.74	1.39

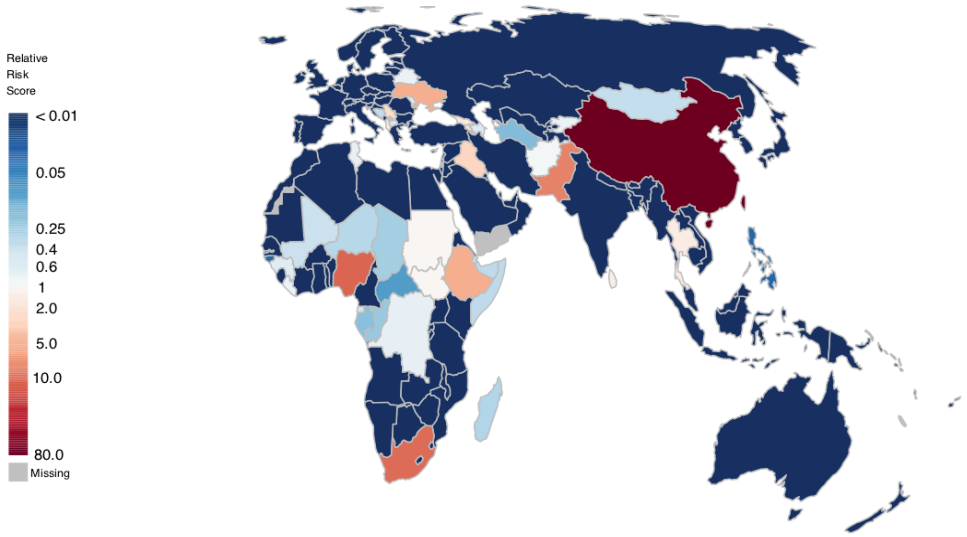
a. Annual force of infection per 1,000 susceptible, estimated from rubella transmission model.
b. Country-level risk for infection among all U.S. based travelers, equal to FOI * annual number of travelers.
c. Relative risk for infection, equal to country-specific risk/mean risk for all countries.
d. Expected infections among U.S. based travelers, equal to risk * proportion susceptible to rubella.

Figure 7. Distribution of rubella force of infection in countries located within WHO regions with endemic transmission.



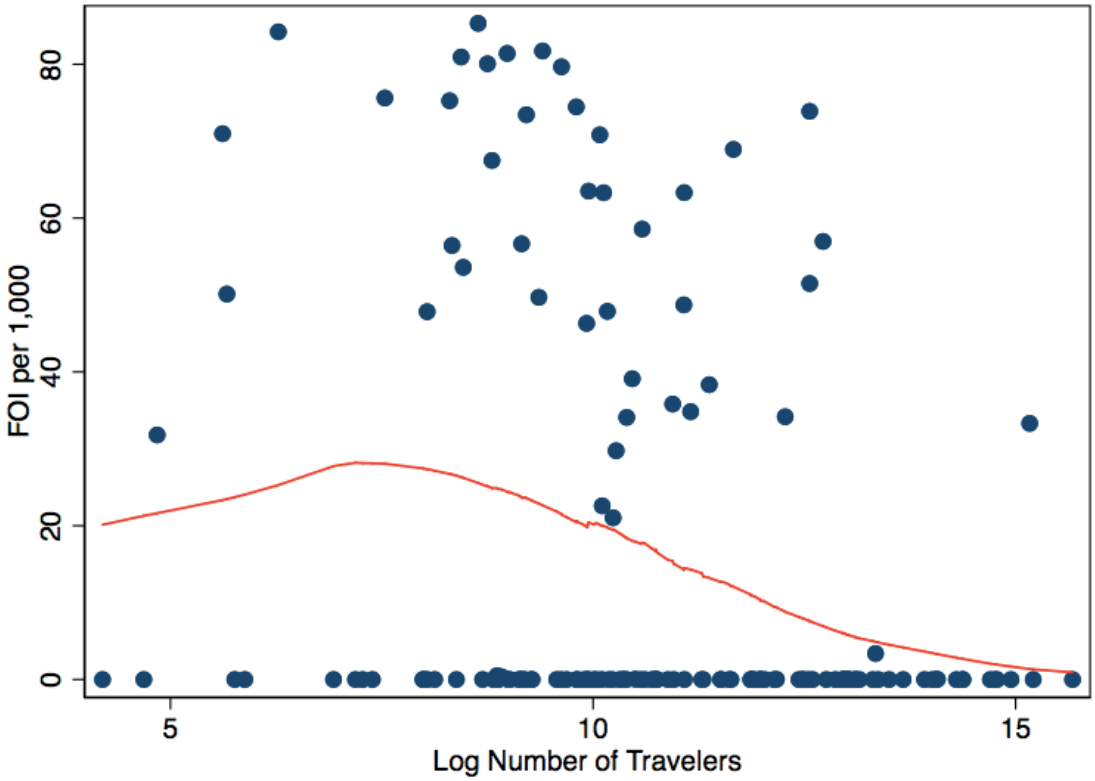
The force of rubella infection varies substantially over the 5 WHO regions that have not yet eliminated rubella. The highest FOIs occur in the African and Eastern Mediterranean Regions, indicating that given susceptibility, the probability of infection is highest in these areas.

Figure 8. Relative risk for rubella in countries located in WHO regions with endemic transmission.



Risk for rubella infection was calculated as the number of travelers to a particular country multiplied by the country-specific force of infection for rubella. The relative risk compares risk across countries by dividing the country-specific risk by the mean risk for all countries. In relative terms, risk of infection is highest in China, followed by Nigeria, South Africa, and Pakistan. Countries in each of the 5 WHO regions studied have relatively high risks for infection, as indicated by the red shading.

Figure 9. Country-level annual force of infection by travel volume from the U.S.



This scatterplot shows the country-level force of infection by log travel volume coming from the U.S. A lowess curve is included to explore the trend in the force of infection with changing travel volume. In general, the force of infection decreases as travel volume increases.

Supplement

Table S1. Participant characteristics, by alternative measure of rubella susceptibility (IgG <8.18 IU/mL).

Characteristic	Susceptible		Immune	
	N[a]	Proportion ± SE (%)[b]	N[a]	Proportion ± SE (%)[b]
Overall (N)	37	2.2 ± 0.4	1,648	97.8 ± 0.4
Age (years)				
18-19	1	0.9 ± 0.9	125	5.3 ± 0.7
20-24	4	14.4 ± 10.4	258	14.6 ± 1.1
25-29	4	10.6 ± 6.7	244	16.1 ± 0.9
30-34	3	8.1 ± 3.1	243	14.8 ± 1.2
35-39	6	9.2 ± 4.6	244	15.5 ± 1.2
40-44	13	39.4 ± 9.1	271	17.6 ± 1.1
45-49	6	17.5 ± 7.6	263	16.2 ± 1.5
Race/ethnicity				
White	16	67.5 ± 9.2	715	60.6 ± 4.1
Black	3	6.0 ± 3.6	291	13.4 ± 1.2
Hispanic	17	25.0 ± 9.4	527	17.0 ± 3.1
Other	1	1.5 ± 1.5	115	8.9 ± 1.4
Born outside of the US	11	23.0 ± 8.6	467	20.2 ± 2.6
Citizenship status				
Citizen	29	88.6 ± 4.6	1,342	87.6 ± 1.9
Not a citizen	7	10.2 ± 4.5	301	12.1 ± 1.9
Refused/Unknown	1	1.2 ± 1.2	5	0.3 ± 0.2
Received hepatitis A vaccine	8	29.3 ± 1.6	522	19.0 ± 7.1

Abbreviations: SE, standard error.
a. N: unweighted number of respondents.
b. Weighted proportion: Proportion of respondents, weighted to account oversampling and non-response.

Table S2. Prevalence and univariable odds ratios of alternative measure of rubella susceptibility (IgG <8.18 IU/mL) among female NHANES participants, aged 18-49 years.

Characteristic	Participants (N)	Prevalence ± SE (%) [a]	OR (95% CI) [a]
Age group, years			
18-19	126	0.38 ± 0.38	0.25 (0.21-3.14)
20-24	262	2.18 ± 1.64	1.50 (0.10-22.37)
25-29	248	1.46 ± 0.84	Ref
30-34	246	1.21 ± 0.41	0.83 (0.19-3.65)
35-39	250	1.32 ± 0.72	0.90 (0.16-4.97)
40-44	284	4.81 ± 1.52	3.42 (0.69-16.92)
45-49	269	2.39 ± 1.15	1.65 (0.33-8.17)
Race/ethnicity			
White	731	2.45 ± 0.51	Ref
Black	294	1.00 ± 0.60	0.4 (0.11-1.48)
Hispanic	544	3.20 ± 0.87	1.32 (0.68-2.54)
Other	116	0.39 ± 0.39	0.16 (0.02-1.26)
Country of birth			
U.S.	1,181	2.13 ± 0.39	Ref
Outside of the U.S.	467	2.49 ± 1.13	1.17 (0.39-3.54)
Citizenship status			
Citizen	1,342	2.23 ± 0.41	Ref
Not a citizen	301	1.87 ± 0.76	0.84 (0.32-2.20)
Refused/Unknown	5	7.87 ± 8.32	3.74 (0.30-45.99)
Received hepatitis A vaccine			
No	1,155	2.52 ± 0.40	Ref
Yes	530	1.44 ± 0.64	0.56 (0.22-1.47)

Abbreviations: SE, standard error, OR, odds ratio; CI, confidence interval; Ref, reference group.

a. NHANES survey weights applied to represent the total U.S. noninstitutionalized population. Accounts for oversampling and non-response.
b. Indicates statistical significance.

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Asher J, Barker C, **Bowles L**, Chen G, Chinazzi M, Cummings DAT, Daniel-Wayman S, Ferguson N, Fischer M, Follman D, Halloran E, Johansson M, Joshi K, Kaminsky J, Keegan L, Kugeler K, Kwan J, Lessler J, Longini I, Monaghan A, Moore S, Pastore y Piontti A, Perkins A, Prevots R, Reich N, Reiner R, Rodriguez-Barraquer I, Siraj A, Sun K, Vespignani A, Zhang Q. (**2017**) Updated Results of Models to Predict Areas in the Americas with Increased Likelihood of Zika Virus Transmission in 2017. *Reported to: Centers for Disease Control and Prevention, September 2017.*

BOOK CHAPTER

Keegan LT, **Bowles L**, Metcalf CJE, Lessler J. Transmission dynamics, modeling of outbreaks and interventions. *Viral Outbreaks, Bioterrorism and Preparing for Mass Casualty Infectious Disease Events,* Elsevier. *In Preparation.*

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